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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

CODE	DATE	NTD
ANKOM 15 APR 2005 GIPS		
DATA ENTERED		
FINAL CHECK		

Applicant's or agent's file reference 100887-1 WO		FOR FURTHER ACTION See Form PCT/IPEA/409
International application No. PCT/SE 2003/002008	International filing date (day/month/year) 18.12.2003	Priority date (day/month/year) 20.12.2002
International Patent Classification (IPC) or national classification and IPC C07D405/06, 405/12, A61K31/4468, 31/4523, A61P1/00, 11/00, 17/00, 19/00 C07D 211/58, 401/06, 401/12,		
Applicant AstraZeneca AB et al		

- This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
- This REPORT consists of a total of 6 sheets, including this cover sheet.
- This report is also accompanied by ANNEXES, comprising:
 - ☐ (sent to the applicant and to the International Bureau) a total of _____ sheets, as follows:
 - ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
 - ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
 - ☐ (sent to the International Bureau only) a total of (indicate type and number of electronic carrier(s)) _____, containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).
- This report contains indications relating to the following items:

<input checked="" type="checkbox"/> Box No. I	Basis of the report
<input type="checkbox"/> Box No. II	Priority
<input checked="" type="checkbox"/> Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
<input type="checkbox"/> Box No. IV	Lack of unity of invention
<input checked="" type="checkbox"/> Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
<input type="checkbox"/> Box No. VI	Certain documents cited
<input type="checkbox"/> Box No. VII	Certain defects in the international application
<input checked="" type="checkbox"/> Box No. VIII	Certain observations on the international application

Date of submission of the demand 22.06.2004	Date of completion of this report 30.03.2005
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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.

PCT/SE 2003/002008

Box No. I Basis of the report

1. With regard to the language, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ This report is based on a translation from the original language into the following language _____, which is the language of a translation furnished for the purposes of:

- ☐ international search (under Rules 12.3 and 23.1(b))
☐ publication of the international application (under Rule 12.4)
☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the elements of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

☒ the international application as originally filed/furnished

☐ the description:

pages _____ as originally filed/furnished

pages* _____ received by this Authority on _____

pages* _____ received by this Authority on _____

☐ the claims:

pages _____ as originally filed/furnished

pages* _____ as amended (together with any statement) under Article 19

pages* _____ received by this Authority on _____

pages* _____ received by this Authority on _____

☐ the drawings:

pages _____ as originally filed/furnished

pages* _____ received by this Authority on _____

pages* _____ received by this Authority on _____

☐ a sequence listing and/or any related table(s) – see Supplemental Box Relating to Sequence Listing.

3. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages _____

☐ the claims, Nos. _____

☐ the drawings, sheets/figs _____

☐ the sequence listing (specify): _____

☐ any table(s) related to the sequence listing (specify): _____

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

☐ the description, pages _____

☐ the claims, Nos. _____

☐ the drawings, sheets/figs _____

☐ the sequence listing (specify): _____

☐ any table(s) related to the sequence listing (specify): _____

* If item 4 applies, some or all of those sheets may be marked "superseded."

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Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application

☒ claims Nos. 14

because:

☒ the said international application, or the said claims Nos. 14
relate to the following subject matter which does not require an international preliminary examination (*specify*):

See PCT Rule 67.1.(iv) : Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. _____
are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. _____ are so inadequately supported
by the description that no meaningful opinion could be formed.

☐ no international search report has been established for said claims Nos. _____

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the
Administrative Instructions in that:

the written form

☐

has not been furnished

☐

does not comply with the standard

the computer readable form

☐

has not been furnished

☐

does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with
the technical requirements provided for in the Annex C-bis of the Administrative Instructions.

☐ See Supplemental Box for further details.

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Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	<u>1-13</u>	YES
	Claims		NO
Inventive step (IS)	Claims		YES
	Claims	<u>1-13</u>	NO
Industrial applicability (IA)	Claims	<u>1-13</u>	YES
	Claims		NO

2. Citations and explanations (Rule 70.7)

The following documents are cited in the search report:

D1 WO 0187839 A1
D2 WO 0076514 A1
D3 WO 02079156 A1
D4 EP 1013276 A1
D5 WO 0192227 A1
D6 EP 903349 A2
D7 WO 9202502 A1

The claimed invention relates to novel piperidine derivatives, which act as modulators of chemokine receptor activity, especially CCR5.

D1 discloses structurally close piperidine derivatives, which act as modulators of chemokine receptor activity, especially CCR5.

The novel piperidine derivatives differ from D1 only in that a $-(CH_2)_n-X-(CH_2)_m$ -chain where X is O or S(O)p is bound to a carbon atom in the piperidine-ring, while in the known compounds an $-N-X$ -chain where X is a direct bond is bound to a carbon atom in the piperidine-ring in the same way. The remaining substitutions in the structure are the same.

D2 discloses structurally close piperidine derivatives, which act as modulators of chemokine receptor activity, especially CCR5.

The novel piperidine derivatives differ from D2 mainly in the substitution on the nitrogen-atom in the piperidine-ring. The

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Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of: BOX V

broken carbon-chain in the claimed compounds, which is bound to a carbon-atom in the piperidine-ring, could be the same as X in D2, when X is -(C0-6 alkyl)-Y-(C0-6 alkyl)- and Y is O, S, SO or SO2.

The compounds in D1 and D2 have the same therapeutical use as the known and thus solve the same problem as the known compounds.

In the light of the prior art and having regarded the present description and claims, the problem underlying the present application is to find further compounds which act as modulators of chemokine receptor activity, especially CCR5.

The solution proposed in claims 1-13 of the present application cannot be considered as involving an inventive step (Article 33(3) PCT) for the following reasons.

It is common practice to synthesise analogues of known compounds. In the present case, D1 as well as this application, may serve as examples.

The selected novel compounds must show an unexpected and advantageous effect over the prior art. No such effect has been demonstrated for the present compounds. In the absence of relevant biological activity data to the support of the compounds, no inventive step can be acknowledged for the entire scope of the claims. The basis for recognition of inventive step of the present compounds over the closest prior art might lie in the assessment that, particularly in the realm of biologically active compounds, even small structural modifications may cause dramatic changes in activity.

However, the structural differences between the compounds of the prior art D1 and the present compounds are at least as great as the structural differences between the latter compounds and the present, structurally more remote compounds.

Thus, claims 1-13 are novel but lack inventive step. The claims have industrial applicability.

D3-D7 disclose the general state of the art and are not considered to be particular relevant.

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Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

Claims 1-4, partly 5 and 6-13 are not supported by the description as required by Article 6 PCT, as their scope is broader than justified by the description and drawings. The reasons therefore are the following: The examples only show some main substituted structures (table I-XIV).